Synthesis, Characterization and Evaluation of Antidiabetic Activity of New Heterocyclic Compounds

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Chapter 1

An outline of the introduction and a quick recap of the process of making and testing heterocyclic compounds for their antidiabetic effects

1.1 Introduction

1.1.1 Antidiabetic Activity

One of the most prevalent degenerative illnesses in the modern world is diabetes mellitus (DM) [1]. DM is a non-communicable condition that is characterized by chronically elevated blood sugar levels resulting from insulin resistance or a lack of insulin. A deficiency of protein tyrosine phosphorylation in the insulin signaling pathway is associated with insulin resistance. As a consequence, reducing significant fluctuations in blood glucose levels is an essential objective in the treatment of individuals who have this metabolic disorder [2]. Glucose is a kind of sugar that is essential for the creation of energy in the cells and organs of the body. On the other hand, insulin, which is a protein hormone that is produced by the pancreas, connects to insulin receptors on a broad range of cells and regulates the amount of glucose in the body. The different physiological processes that take place in our biological systems need energy, which is produced by the metabolism of glucose in the cells. Insulin helps our systems to effectively use and store carbohydrates while regulating blood glucose levels. Diabetes occurs when our bodies do not produce enough insulin, which is necessary for cells to utilize glucose. As a result, glucose accumulates excessively in the blood [3]. Diabetes is a metabolic disorder that arises from a number of different factors, including insulin resistance, an insufficient production of insulin, and genetic abnormalities in pancreatic beta-cells. In addition to advanced age, other variables that contribute to the illness include being overweight and leading a sedentary lifestyle. When an individual gets diabetes, their bodies either fail to produce sufficient amounts of insulin or are unable to use it appropriately. It has been shown that oral hypoglycemic medicines that block the saccharide hydrolyzing enzyme alpha-amylase are beneficial in managing hyperglycemia in individuals with type 2 diabetes.

Types of Diabetes mellitus

There are mainly two types of diabetes, namely

Type I: Insulin-dependent diabetes mellitus (IDDM), in which the cause is an absolute lack of insulin secretion.

TypeII:Non-insulin-dependent diabetes mellitus (NIDDM), in which the cause is a combination of insulin resistance and an insufficient compensatory insulin secretory response[4,5].

Hyperglycemia is the defining characteristic of diabetes mellitus (DM), which is a complex illness [6]. Elevated oxidative stress is responsible for damage to pancreatic beta cells [7], a fault in the enzymes that scavenge reactive oxygen species [8], and higher metabolic rate during rest as well as anomalies in lipoproteins [9,10]. It is characterized by persistent hyperglycemia and irregularities in the metabolism of carbohydrates, lipids, and proteins. It has been shown that high oxidative stress and chronic hyperglycaemia are connected to the development and onset of long-term complications such as cardiovascular disease, retinopathy, nephropathy, and neuropathy in patients who have diabetes [11]. One of the most serious chronic microvascular complications of diabetes is diabetic nephropathy; it has eclipsed kidney failure as the major cause of end-stage renal disease.

Diabetes has spread over the globe, reaching the proportions of a pandemic. that the current number of people who have diabetes, which is over 220 million, may potentially double by the year 2030 [12]. Despite the fact that the majority of patients with type 2 diabetes are prescribed anti-diabetic drugs, they are unable to maintain sufficient glycemic control and subsequently develop microvascular and macrovascular problems associated with diabetes [13,14]. A group of chronic metabolic diseases known collectively as diabetes mellitus are defined by the presence of consistently increased amounts of glucose in the blood [15].

The suppression of alpha amylase enzyme slows carbohydrate digestion and lengthens total carbohydrate digestion time, resulting in a slower rate of glucose absorption and a lower postprandial plasma glucose spike. For a long period of time, diabetic patients have been treated using heterocyclic chemicals. Medications such as sulfonylurea and biguanides reduce hyperglycemia in individuals who have diabetes. Nevertheless, the continuous search for alternative drugs for the purpose of controlling diabetes continues to be a challenge for medicinal chemists [16,17]. Abnormalities in the production of insulin, the action of insulin, or both are responsible for the development of diabetes mellitus, which is a metabolic disorder [18]. In addition, individuals with diabetes are more susceptible to developing illnesses of the

cardiovascular, cerebrovascular, and peripheral systems [19]. Abdominal obesity, hypertension, hyperlipidemia, and increased coagulability are all symptoms that fall under the umbrella of metabolic syndrome [20]. New medicines that are both safer and more successful are going to take longer to investigate since DM is a chronic illness that requires long-term maintenance [21].

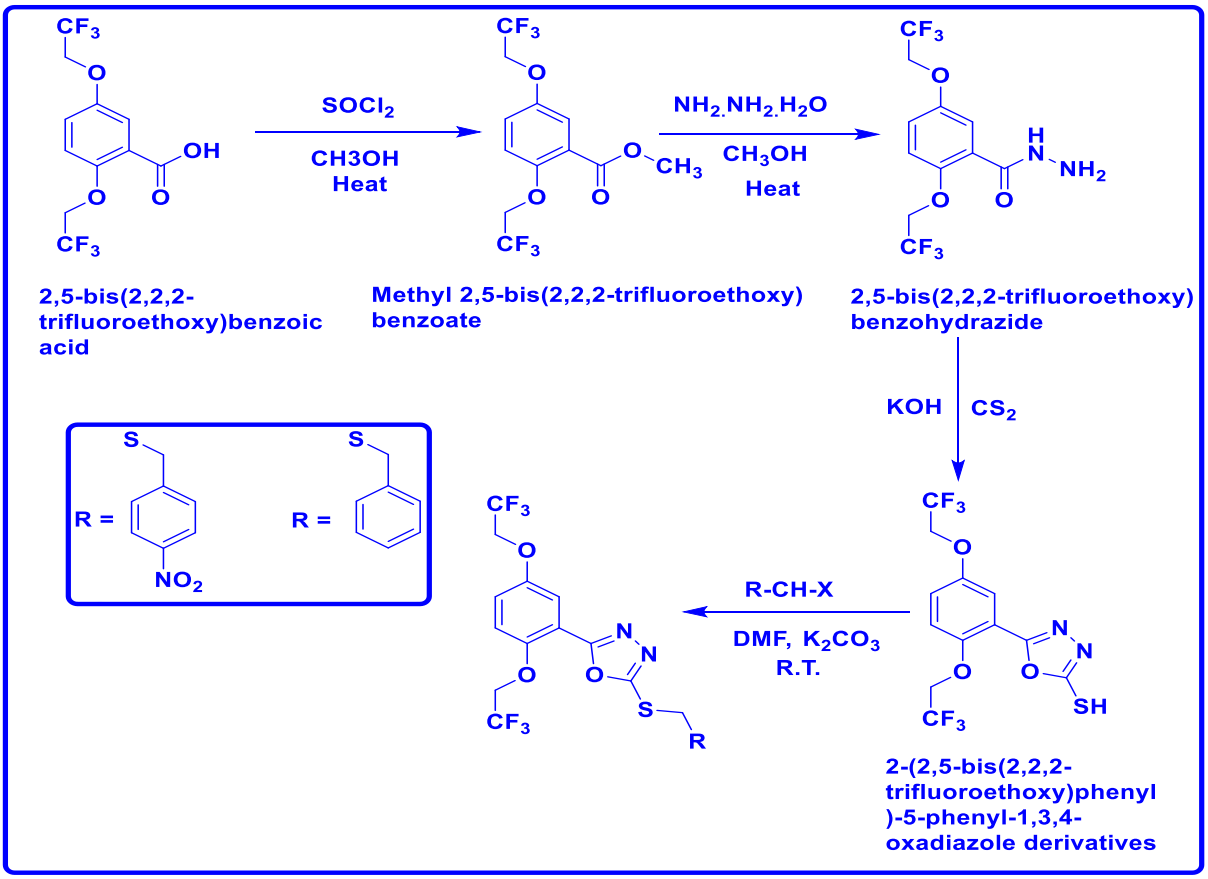
It is anticipated by the World Health Organization (WHO) The number of diabetes was predicted to be 451 million in 2017, and that number is expected to increase to 693 million by the year 2045 [12]. As a result, diabetes has become a worldwide epidemic affecting public health. It is very essential to control this pandemic in the current scenario in order to protect the interests of the generations who will come after us. The scientific community must confront this situation and provide remedies immediately. Consequently, we have chosen the study subject entitled "Synthesis, Characterization, and Evaluation of Antidiabetic Activity of New Heterocyclic Compounds."

1.1.2 Enzymes: Molecules that are used in medicine called enzyme inhibitors attach to enzymes that are involved in the metabolism of glucose. The brush border of the small intestine contains both α-glucosidase and α-amylase enzymes, which break down carbohydrate into little glucose units by means of hydrolysis. These enzymes raise the levels of postprandial blood glucose. As a result of this impact, these enzymes have become principal targets for the creation of medicines to treat diabetes [22]. New chemicals that block the action of these enzymes decrease the amount of glucose that is absorbed from the small intestine, which results in lower levels of postprandial blood glucose and contributes to the treatment of diabetes. A number of treatment methods have been established for diabetes. Of particular importance to contemporary therapy approaches are carbohydrate-hydrolyzing enzymes such as α-glucosidase and α-amylase [23,24]. α-Glucosidase is an enzyme that catalyzes the hydrolysis of α-1,4-glucoside linkages in oligosaccharides, resulting in the production of monosaccharides that are digestible [25,26]. It is possible to lessen postprandial hyperglycemia by decreasing the uptake of glucose units and blocking this enzyme [27–30].

1.2 Antidiabetic activities of heterocyclic compounds

Heterocyclic compounds, particularly those that include nitrogen, sulfur, and oxygen, have found important uses in the pharmaceutical industry, the agricultural industry, and other sectors [31]. One of the most prominent categories in the domain of pharmaceutical chemistry

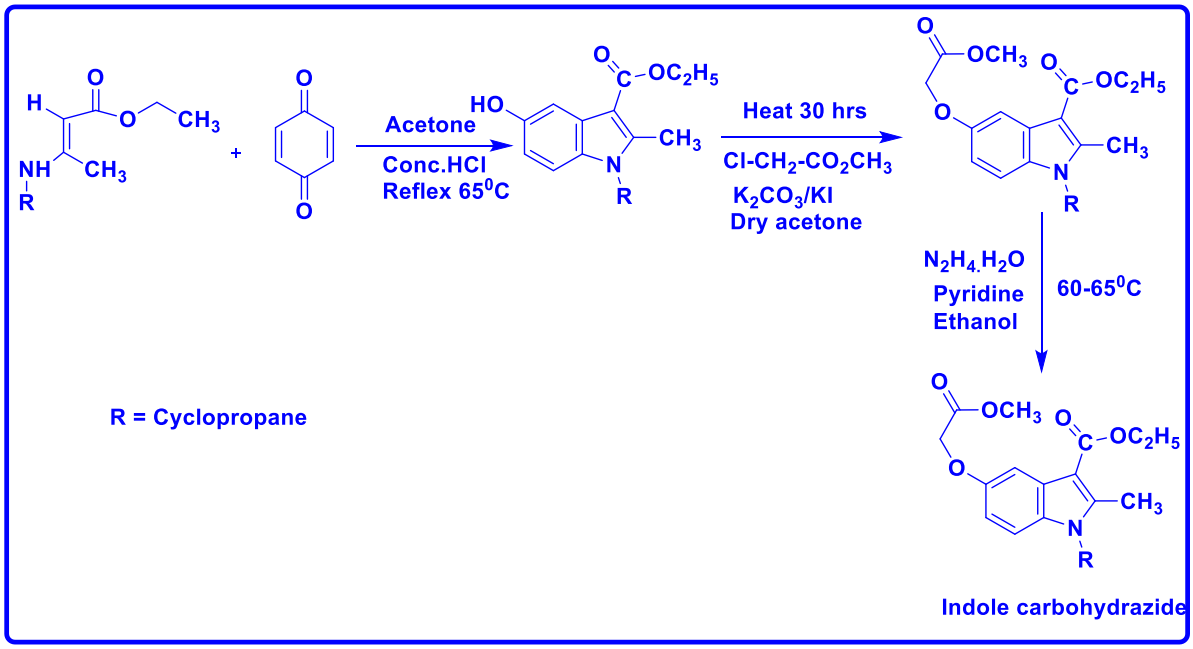
is that of the derivatives of oxadiazole. The area of novel drug discovery research has seen a major growth in recent times. This advancement shows that there is a substantial role for the use of combinatorial pharmaceuticals in pharmaceutical chemistry. It is desirable to mix two or more pharmacophore moieties with unique physiologically active chemicals in order to develop a hybrid medication that demonstrates increased affinity and effectiveness in contrast to the conventional [32]. Recently, there has been a great deal of interest in the biological and pharmacological aspects of heterocyclic molecules and their derivatives. The 1,3,4-oxadiazole derivatives are members of a heterocyclic family that has promising uses in the field of medicines [33]. Antihyperglycemic activities have been shown in 1,3,4-oxadiazole derivatives, according to the findings reported in the literature. We have carried out a study of the literature about the synthesis, characterization, and antidiabetic properties of indole, triazole, and pyrazole derivatives in a similar fashion. On the basis of these literature study reports, we have devised synthetic routes for the synthesis of new heterocyclic compounds.



Scheme 1.1 Synthesis of 5-(2,5-bis(2,2,2-trifluoroethoxy)phenyl)-1,3,4-oxadiazole-2-thiol derivatives

Heterocyclic chemistry is an important branch of organic chemistry, and it is responsible for the production of several novel chemical entities. These new chemical entities account for more than one-third of the current publications in a wide range of magazines [34]. The chemical compound known as indole is categorized as a heterocyclic aromatic organic molecule. The structure of indole is composed of a pyrrole ring and a benzene ring that are fused together. It is distinguished from other compounds that are heterocyclic due to its unique characteristics. There are a wide range of therapeutic actions that indole derivatives demonstrate; they include antiviral, antifungal, anthelmintic, anticonvulsant, antitubercular, antihistamine, cardiovascular, antibacterial, antidiabetic, depressive, anti-inflammatory, and other qualities [35].

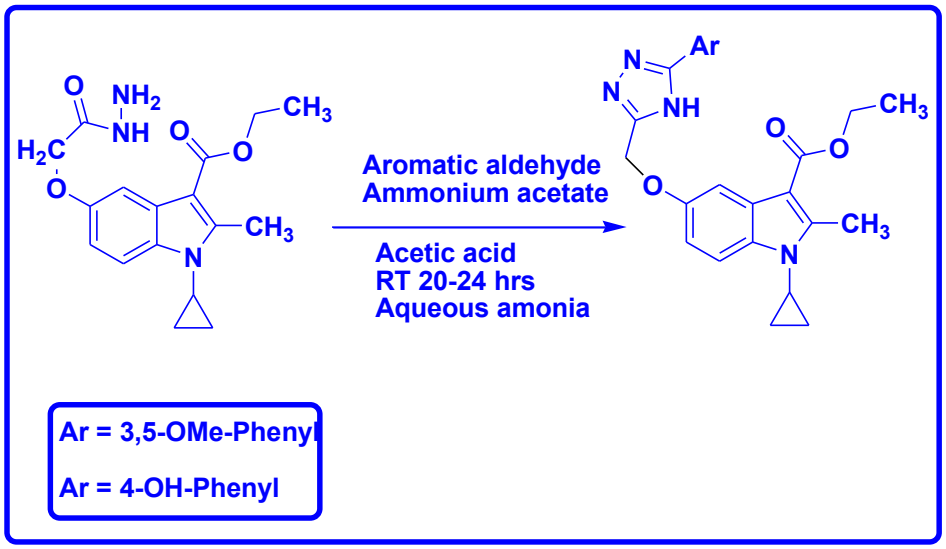
In light of the intriguing biological activities exhibited by oxadiazole and in furtherance of our research on the chemoselectivity of indole carboxylate towards hydrazine hydrate, as illustrated in the following **Scheme 1.2**



Scheme 1.2 Synthetic route of indole carbohydrazide

They have lately carried out study and explored the fact that triazoles, which are *N*-substituted heterocyclic compounds, have been proved to have antidiabetic characteristics. In a recent demonstration, it was shown that derivatives of 4-amino-1,2,4-triazole, which include a range of aldehydes, have good *in-vitro* inhibitory actions for α-glucosidase and α-amylase [36]. When compared to ordinary acarbose, hybrid heterocycles that are made up of benzothiazole-triazole derivatives were shown to have modest α-glucosidase inhibitory action [37]. As a

result, the pharmacological potential of fused-heterocyclic compounds comprising indole and 1,2,4-triazole, as well as their importance in biological processes, has made them very interesting candidates for investigation. We have performed a synthesis of a diverse assortment of 1,2,4-triazole derivatives that include the indole moiety, and we have subsequently carried out an evaluation of their inhibitory ability against α-amylase and α-glucosidase via the use of *in-vitro* and in silico approaches, which were based on the previously given necessary facts.



Scheme 1.3 Synthetic route of indole triazole derivatives

1.3 Antidiabetic drugs present in market

A large number of antidiabetic drugs are now available on the market with the purpose of treating hyperglycemia. These medications function by boosting insulin sensitivity, supplementing insulin, raising insulin production, and promoting the uptake of glucose into the body. In order to keep blood glucose levels under control and avoid problems, antidiabetic drugs are necessary for the treatment of diabetes. They operate by boosting insulin sensitivity, increasing insulin secretion, or lowering the synthesis and absorption of glucose in the body. There are several types of antidiabetic medications, and each of them targets a different mechanism in order to achieve these goals. Every single one has its own set of qualities, advantages, and disadvantages. In addition to this, each class targets a different mechanism; each of these mechanisms has its own set of features and possible adverse effects. Acarbose, miglitol, and voglibose are only a few examples. Acarbose, miglitol, and voglibose are the names of the three medications that can be bought commercially and are used to treat

diabetes; all three of these medications are derived from natural sources. **Table 1** displays the chemical structures of acarbose, miglitol, and voglibose, as well as their respective structures.

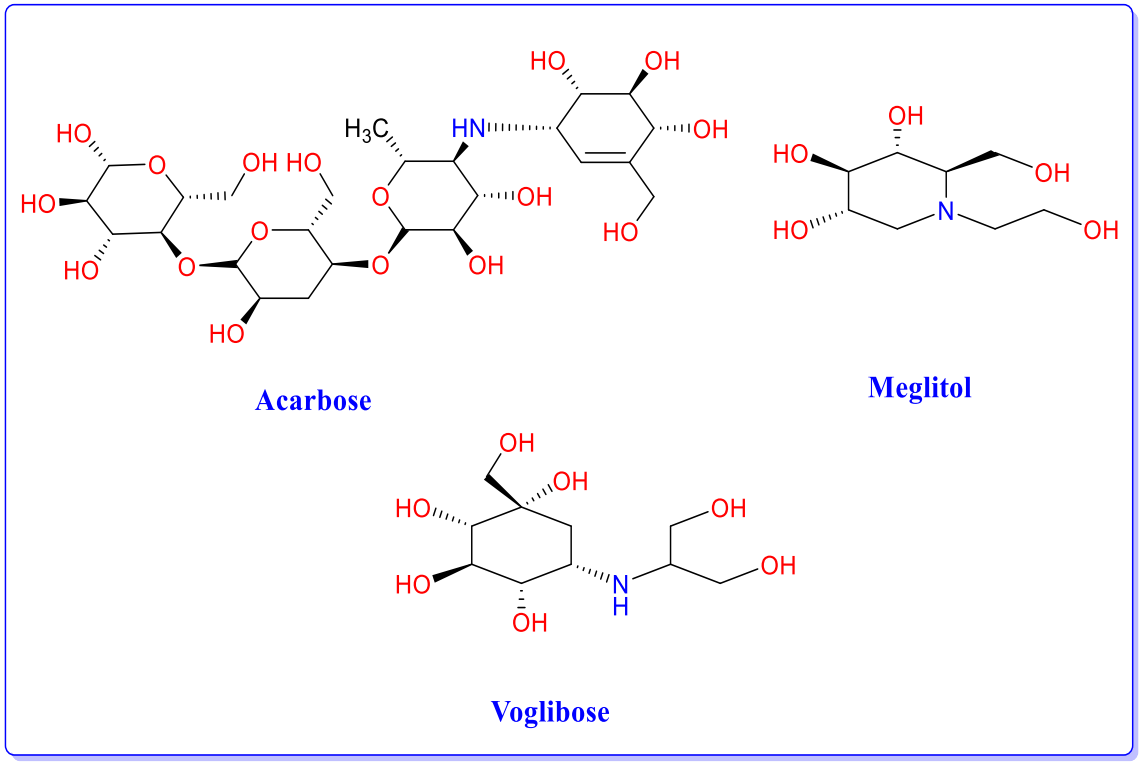


Table 1 Oral antidiabetic drugs available in the market and contain OH, and NH groups

1.4 Protocol for *in-vitro* and *in-vivo* study of antidiabetic activity

1.4.1 To determine α-amylase inhibition assay

Distilled water was used to make stock solutions of samples as well as of acarbose. As previously detailed, with a few adjustments, the dinitrosalicylic acid (DNS) method was used to evaluate the suppression of porcine α-amylase activity [38]. In order to get a final concentration of between 0.5 and 5 mg/ml, 100 µl of α-amylase (1 U/ml) and 200 µl of sodium phosphate buffer (20 mM, pH 6.9) were combined with 100 µl of synthesized compounds or acarbose (2 to 20 mg/ml). After being pre-incubated at a temperature of 25°C for a duration of 10 min, 200 ml of 1% starch that had been produced in a 20 mM sodium phosphate buffer (pH 6.9) were added to the samples. The reaction mixtures were let to sit at a temperature of 25°C for a period of 10 min. Following the addition of 1ml of dinitrosalicylic acid, the mixture was incubated in a boiling water bath for a period of 5 min, which effectively terminated the processes that were taking place. The absorbance of the reaction mixtures was measured using a spectrophotometer at a wavelength of 540 nm after the

mixtures were cooled to room temperature and diluted with water in a 1:5 ratio. The calculation of the percentage of inhibition of enzyme activity was determined as follows:

$$\% \text{ Inhibition} = [(A_{540}^{Control} - A_{540}^{Treated})/A_{540}^{Control}] \times 100$$

Where in $A_{540}^{Control}$ is the absorbance at 540 nm in control and $A_{540}^{Treated}$ is the absorbance at 540 nm in reaction mix with the compounds

1.4.2 To determine α-glucosidase inhibition assay

A previously published method was followed in order to measure the extent of α-glucosidase activity inhibition. The method made use of yeast α-glucosidase and p-nitrophenyl-α-D-glucopyranoside (pNPG) [39].To achieve a final concentration of 0.5 to 5 mg/ml, 100 µl of synthesized compounds or standard acarbose (with a concentration of 2 to 20 mg/ml) was added to 50 µl of α-glucosidase (1 U/ml) that had been made in 0.1 M phosphate buffer (pH 6.9), as well as 250 µl of 0.1 M phosphate buffer. Prior to the commencement of the experiment, the mixture was incubated at a temperature of 37°C for a period of 20 min. 10 ml of 10 mM pNPG produced in 0.1 M phosphate buffer with a pH of 6.9 were added after pre-incubation. After that, the mixture was incubated at 37°C for 30 min. After the addition of 650 µl of sodium carbonate with a molarity of 1 M, the reactions were terminated, and a spectrophotometer was used to detect the absorbance at 405 nm. The calculation of the percentage of inhibition of enzyme activity was determined as follows:

$$\% \text{ Inhibition} = [(A_{405}^{Control} - A_{405}^{Treated})/A_{405}^{Control}] \times 100$$

Where in $A_{405}^{Control}$ is the absorbance at 405 nm in control and $A_{405}^{Treated}$ is the absorbance at 405 nm in reaction mix with the compounds.

1.4.3 To molecular docking studies

Molecular modeling was performed using Sybyl-X, version 2.0 [40], which was run on an Intel® CoreTMi3-2130 CPU@ 3.40 GHz processor that was running the Windows 7 professional workstation operating system. Docking of the compounds that were created was

carried out using the Surflex-Dock algorithm of Sybyl-X 2.0. Initial docking studies were conducted using the crystal structure of the *N*-terminal subunit of human maltase-glucoamylase in complex with acarbose. The crystal structure was downloaded from the Protein Data Bank (PDB entry code 2QMJ; X-ray diffraction; 1.9 Å). The Brookhaven Protein Database (http://www.rcsb.org) was the source of the PDB from which the crystal structure was extracted. The structure was treated in such a manner that the co-crystallized ligand and water molecules were eliminated, necessary hydrogen atoms were added, and side chains were fixed over the course of protein synthesis. Following that, the structure was exposed to a process of energy refining. The Gasteiger-Hückel method was utilized to determine the charges for the ligand [41], whereas the Amber 7 FF02 force field was employed for the protein [42]. The Powell method's gradient termination was used to submit the model to energy reduction for a total of 3000 iterations. During this process, the Tripos force field was used, the non-bonding cut-off was established at 9.0, and the dielectric constant was set at 4.0. A number of scoring functions that have been combined into the single consensus score (CScore) were also used to estimate the binding of the substituted oxadiazole derivatives.

1.4.4 To evaluate antidiabetic activity of new compounds using *Drosophila* model

Wild type Canton-S flies were procured from the *Drosophila* Stock Centre at Mysore University, India, and were reared on wheat cream-agar medium at a temperature of 25^0C, relative humidity of 65–70 %, and a light–dark cycle of 12:12 hours. After being separated, male and female flies that were one day old were reared in a nutrient-rich environment that included a consistent quantity of the compounds or acarbose, which served as a positive control, for a period of 10 days. The concentration of the compounds in the feed was 18 µg/g. The twenty flies were collected and placed in 0.5 ml of phosphate-buffered saline (pH 7.4) that was kept on ice. The flies were then homogenized. The samples that had been homogenized were centrifuged for 15 min at a temperature of 4^0C and with a force of 10,000 g. A commercially available kit was used to determine the glucose levels in the fly homogenate following the manufacturer's instructions (Agappe Diagnostics Ltd, India). The concentration of glucose was expressed as milligrams per deciliter (per fly).

1.5 Aims and objectives of the present research work

The aims and objectives of the present research work were expressed in the following way,

- To synthesize new heterocyclic compounds, including oxadiazole, indole, and triazole pyrazole, among others.
- To characterize the structure of newly synthesized compounds, using ^{1}H-NMR, ^{13}C-NMR, FT-IR, and Mass spectroscopic techniques.
- To evaluate the antidiabetic efficacy of α-amylase and α-glucosidase *in-vitro* inhibition experiments and to compare the results of these evaluations to the reference medication, which is acarbose, a substance that is currently used in the pharmaceutical business.
- To forecast the binding affinity of ligands to receptor proteins by conducting molecular docking studies of molecules that have just been produced.
- To ascertain the survival rate, capacity to climb, and glucose level in the hemolymph of *Drosophila melanogaster* after the ingestion of highly antidiabetic activated produced substances.
- To create a cost-effective technique for the evaluation of antidiabetic efficacy utilizing the *Drosophila melanogaster* model.

1.6 Research Gap

- The introduction of a significant number of heteroatoms in conjunction with heterocyclic compounds may be a suitable method to boost both stability and bioactivity. It is necessary to fill this gap in the research by manufacturing fused heterocyclic compounds that use a significant number of heteroatoms.
- The digestion of food is expedited by α-amylase and α-glucosidase, which also raise postprandial blood glucose levels. As a result, these essential enzymes are promising candidates for the creation of medications that may be used to treat diabetes. It is possible to block or extend the digestion of carbohydrates and slow the rate of glucose absorption from insulin by employing fused heterocyclic molecules that include a high number of substituted nitrogen, oxygen, and sulfur atoms. We have predicted these molecules may have the ability to regulate hyperglycemia.

- In clinical practice, medications such as voglibose, miglitol, and acarbose are now being used. Because of this occurrence, these medicines may attach themselves to enzymes such as α-amylase and α-glucosidase in a reversible manner, which results in an increase in the number of side effects that they produce. In order to address this problem, the number of side effects should be reduced. In order to get effective antidiabetic medications, we may need to make use of a variety of heterocyclic compounds and adopt a combination treatment.
- There is a growing number of adverse effects associated with currently available medications. Consequently, we must focus our efforts on synthesizing novel heterocyclic compounds that are less toxic and more effective.

1.7 Motivation for the proposed research work

- **Reason 1:** A large number of polyhydroxyl and NH groups and produce adverse effects are found in the vast majority of drugs on the market for decreasing blood sugar levels, we have utilized our creativity to come up with new heterocyclic molecules that include a large amount of oxygen and nitrogen. In addition, we have concentrated our efforts on gaining a knowledge of how enzyme inhibitory activity is impacted by the presence of other groups, such as fluorine, chlorine, methoxy groups, and so on.

- **Reason 2:** According to estimates provided by the World Health Organization (WHO), The number of diabetes was predicted to be 451 million in 2017, and that number is expected to increase to 693 million by the year 2045. As a result, diabetes has become a worldwide epidemic affecting public health. It is very essential to control this pandemic in the current scenario in order to protect the interests of the generations who will come after us. As a result, the scientific community must rapidly deal with this situation and find solutions.
- Because of the two criteria described above, we picked suggested research entitled "Synthesis, Characterization, and Evaluation of Antidiabetic Activity of New Heterocyclic Compounds."

Chapter 2

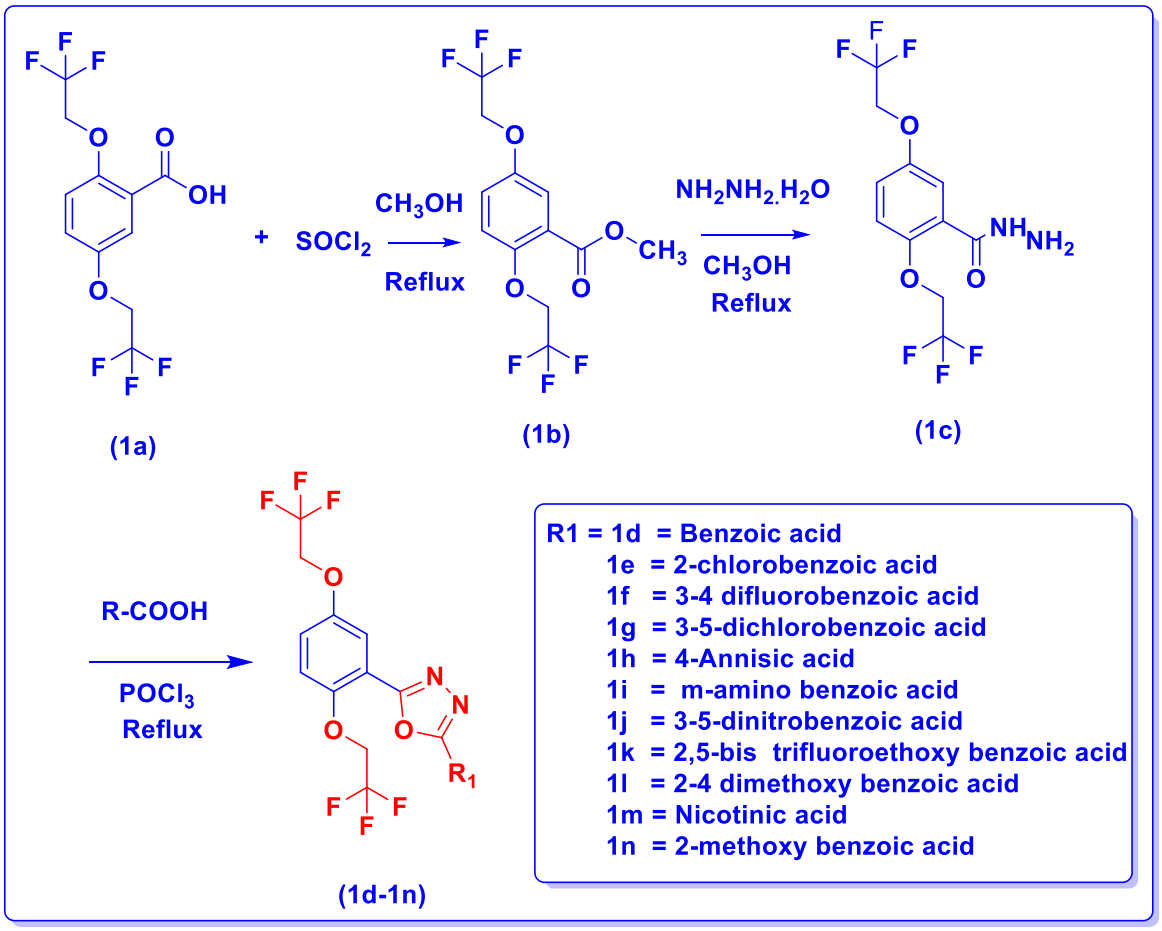
Synthesis and characterization of oxadiazole derivatives; *in-vitro* and *in-vivo* assessment of their antidiabetic efficacy using the *Drosophila melanogaster* model

2.1 Introduction

The process of producing novel pharmaceuticals has recently garnered much more attention to the hybridization method, which has served as a source of inspiration in this endeavor. The concept of hybrid molecules is created by joining together a minimum of two active pharmacophores to generate a single hybrid molecule. Flecainide is a medication that is used to treat and prevent excessively fast heartbeat. It is constructed of a piperidylmethyl group and 2,5-bis (2,2,2-trifluoroethoxy benzoic acid). The inhibitory action of new oxadiazole compounds synthesized by Gani et al., that included the 2,5-bis (2,2,2-trifluoroethoxy) group was evaluated by the researchers using α-amylase and α-glucosidase. This study used a hybridization process that included the use of flecainide and compounds that are structurally similar to flecainide. The purpose of this technique was to synthesize new derivatives of 1,3,4-oxadiazole that included a 2,5-bis (2,2,2-trifluoroethoxy) moiety.

2.2 Materials and Methods

The fluorine-incorporated 1,3,4-oxadiazole derivatives (**1c-1n**) were produced and analyzed using ^{1}H-NMR, mass, and FT-IR spectroscopy. They were also examined for α-amylase and α-glucoside enzyme inhibition activities. The antidiabetic properties of the substance were investigated utilizing an *in-vivo Drosophila melanogaster* model and an *in-vitro* system, and density functional theory (DFT) was applied to generate more geometrically optimized molecule structures by employing the B3LYP technique.



Scheme 2.1 Synthesis of 2-(2,5-bis(2,2,2-trifluoroethoxy)phenyl)-5-phenyl-1,3,4-oxadiazole derivatives

2.3 Results and Discussion

The substances were examined to determine their effectiveness against the α-glucosidase and α-amylase enzymes. Out of the various compounds that were subjected to testing, compounds **1i** (IC_{50} = 54.83 µg/ml), **1k** (IC_{50} = 64.95 µg/ml), **1m** (IC_{50} = 64.78 µg/ml), and **1n** (IC_{50} = 66.30 µg/ml) demonstrated significant efficacy as α-amylase inhibitors in comparison to acarbose (IC_{50} = 35.17 µg/ml); compounds **1m** (IC_{50} = 74.64 µg/ml) and **1i** (IC_{50} = 60.35 µg/ml) exhibited significant α-glucosidase inhibitory action in comparison to acarbose (IC_{50} = 46.06 µg/ml). It was shown by the docking investigation that the active site of the enzyme (PDBID: 4w93) makes six hydrogen bonds with compound **1i** and three hydrogen bonding interactions with compound **1m**.

2.4 Conclusion

New 1,3,4-oxadiazole compounds that include fluorine were manufactured and identified by use of spectroscopic analysis methods. The findings suggest that compounds **1i**, **1m**, **1n**, and **1k** exhibit stronger antidiabetic activity and, as a consequence, should be taken into further consideration for antidiabetic therapeutic treatments.

Chapter 3

Synthesis, characterization, α-amylase, α-glucosidase inhibition, and molecular modelling investigations of some indole and pyrazole derivatives

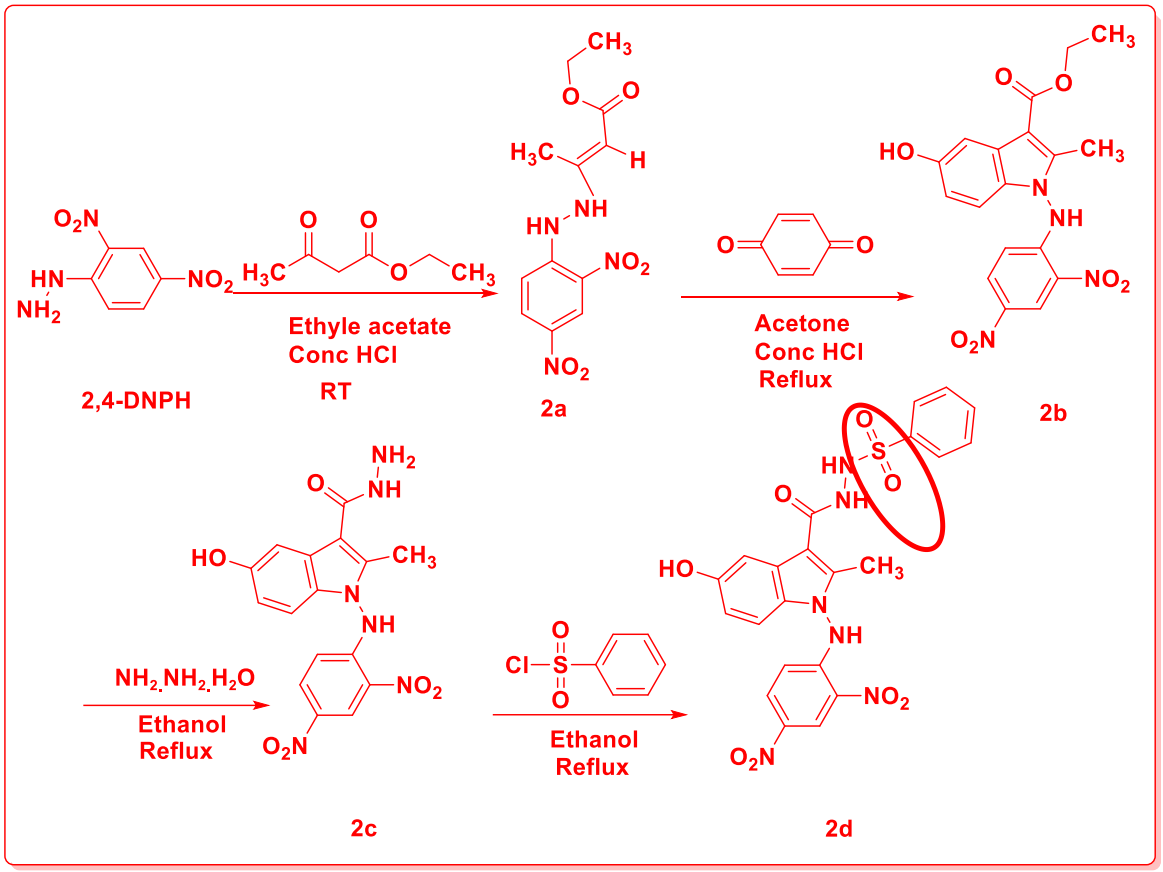
3.1 Introduction

In order to assess its antidiabetic qualities, the chapter defined a distinct heterocyclic molecule that had both indole and pyrazole since the majority of current antidiabetic medications did not possess these specific components. Polyhydroxy groups are found in the majority of α-amylase and α-glucosidase inhibitors, including voglibose, miglitol, and acarbose, among others. These chemicals, on the other hand, are known to often cause gastrointestinal side effects. On the other hand, we use functional groups that include chlorine, fluorine, nitrogen, and oxygen, as opposed to polyhydroxy groups. We also make use of heterocyclic compounds, such as pyrazole and indole. In order to place emphasis on the significance of other functional groups, we focused our efforts on the development of a limited number of molecules that lacked polyhydroxy groups. The production of the compounds (**2f-2g**) and (**2a-2d**) was accomplished via the use of this method. Our previous research indicates that hybrid molecules have a substantial role in the inhibition of the enzymes α-amylase and α-glucosidase.

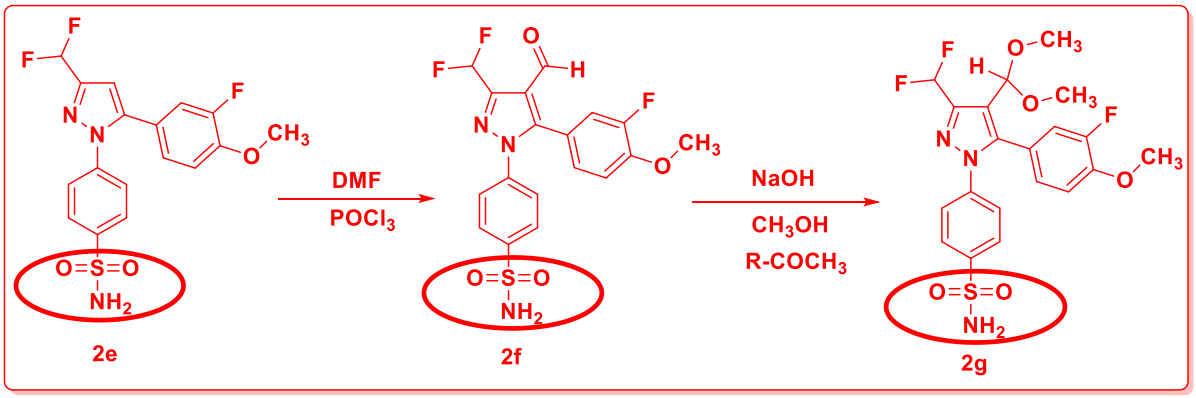
3.2 Materials and Methods

Mass spectrometry, ^{1}H-NMR, ^{13}C-NMR, and Fourier transform infrared spectroscopy (FT-IR) were used to investigate the newly synthesized sulfonamide-based indole and pyrazole derivatives. Utilizing *Drosophila melanogaster* as a model organism, research was conducted in order to evaluate the toxicological and antidiabetic properties of the organism both *in-vitro*

and *in-vivo*. For the purpose of doing molecular modeling research, Sybyl-X version 2.0 was used.



Scheme 3.1 Synthesis of sulphonamides-based Indole derivatives



Scheme 3.2 Synthesis of sulphonamides-based pyrazole derivatives

3.3 Results and Discussion

According to the results, compound (**2d**) (IC_{50} = 83.87 µM for α-amylase and IC_{50} = 73.15 µM for α-glucosidase) and compound (**2g**) (IC_{50} = 63.34 µM for α-amylase and IC_{50} = 80.92 µM for α-glucosidase) exhibited significant enzyme inhibitory activities compared to acarbose, the positive control (IC_{50} = 35.17 µM). Furthermore, the absorption, distribution, metabolism, and excretion (ADME) characteristics of the compounds that had been produced were investigated with the use of the SwissADME online tool. A continuation of study may be carried out on the chemicals (**2g**) and (**2d**) to investigate their potential as new antidiabetic medicines by systematically increasing the dosage. This may improve their therapeutic effectiveness.

3.4 Conclusion

This chapter discusses a reaction that provides a feasible and systematic strategy for the production of a novel class of indole-pyrazole derivatives that are based on sulfonamides. The results suggest that the compounds (**2d**) and (**2g**) have the potential to be further developed into new antidiabetic medications and that they may be candidates for clinical trials in the future.

Chapter 4

Synthesis, characterization, evaluation of *Drosophila* model-based enzyme inhibitory activity of crotonate-based 1,2,4-triazole derivatives

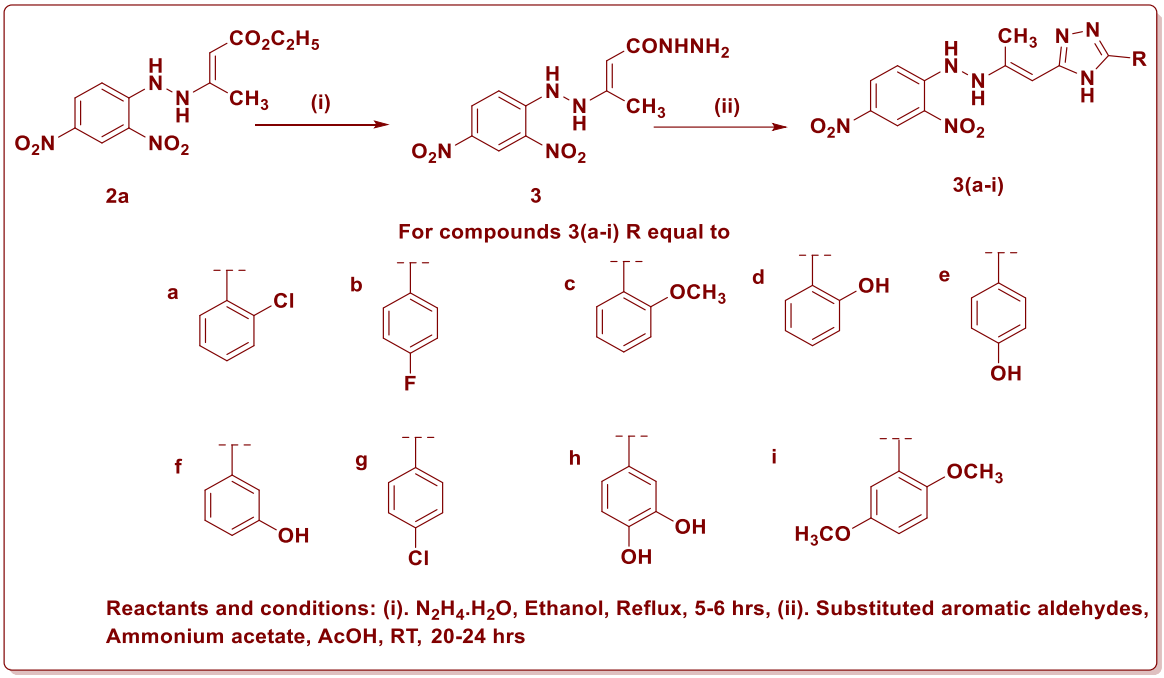
4.1 Introduction

The 1,2,3-triazole and 1,2,4-triazole ring structures are found in compounds that have been shown to possess a broad spectrum of biological activities, including features that are effective in the treatment of diabetes. Azoles, particularly 1, 2, and 4-triazoles, are widely known for being well-tolerated urease inhibitors that also have anti-diabetic properties. The antidiabetic properties of triazoles, which are molecules that have an *N*-substitution and a heterocyclic structure, as well as the substantial *in-vitro* inhibitory activity of 4-amino-1, 2, and 4-triazole derivatives when they are combined with a variety of aldehyde compounds,

have been shown by the findings of research that was conducted recently. The α-glucosidase activity was somewhat reduced when exposed to heterocycles that were made up of benzothiazole-triazole derivatives. A group of substituted 1,2,4-triazole-3-thione derivatives has the ability to inhibit both α-amylase and α-glucosidase. Researchers found that a 2-6-di(substituted phenyl)thiazole [3,2-b]-1,2,4-triazole was successful in efficiently inhibiting the enzymes α-amylase and α-glucosidase. Additionally, research indicated that in contrast to normal acarbose, a variety of derivatives, including indolyl xanthene, indole carbohydrazide, indole hydrazone, and triazoles, exhibited inhibitory effects. Because of this, heterocyclic compounds that include the 1-(2,4-dinitrophenyl)-2-(prop-1-en-2-yl)hydrazine, phenyl moiety, and 4*H*-1,2,4-triazole, as well as their pharmacological potential and biological importance, have become very desired study topics. The information provided above was taken into consideration, and on the basis of that information, we devised **Scheme 4.1** and synthesized a variety of 1, 2, and 4-triazole derivatives containing a phenyl moiety. These derivatives were also assessed for their ability to block the enzymes α-amylase and α-glucosidase using *in-vitro* and *in-vivo* techniques.

4.2 Materials and Methods

The goal of this research endeavor is to synthesize a variety of 1,2,4-triazole derivatives (**3a–3i**) that include the compound (*E*)-3-(2-(2,4-dinitrophenyl)hydrazinyl)prop-1-en-1-yl. Additionally, spectroscopic techniques, such as ^{1}H-NMR, ^{13}C-NMR, FT-IR, and LC-MS, were used to verify the identities of the synthesized compounds. The anti-diabetic potential of the compounds was evaluated by measuring the levels of α-amylase and α-glucosidase enzyme inhibition *in-vitro* and *in-vivo*. In addition, optimal molecular structures of the compounds generated using DFT at the B3LYP/6-311G(d,p) level of theory were determined.


2a
3
3(a-i)
For compounds 3(a-i) R equal to
Reactants and conditions: (i). $N_2H_4.H_2O$, Ethanol, Reflux, 5-6 hrs, (ii). Substituted aromatic aldehydes, Ammonium acetate, AcOH, RT, 20-24 hrs

Scheme 4.1 Synthesis of crotonate-based 1,2,4-triazole derivatives

4.3 Results and Discussion

The triazole ring and the benzyl moiety, which may comprise the following groups: hydroxyl (OH), fluorine (F), chlorine (Cl), or methoxy (OCH3), are the primary factors that determine the inhibitory action of α-amylase and α-glucosidase. An IC_{50} value of 64.39 µg/ml was found for compound **3b**, which exhibited elevated α-amylase activity. With an IC_{50} value of 65.74 µg/ml, compound **3a** exhibited the second-highest level of α-amylase inhibitory action. The second highest efficacy in the inhibition of α-glucosidase was shown by compound **3a**, which has an IC_{50} value of 77.31 µg/ml. The most promising candidate for the role of an α-glucosidase inhibitor was compound **3b**, which had an IC_{50} value of 76.48 µg/ml. Compound **3a**, which contains an ortho-substituted benzene ring and an electron-drawing chlorine, was shown to be the second most potent inhibitor of α-glucosidase, with an IC_{50} value of 77.31 µg/ml. Further, ADME properties of the synthesized compounds were analyzed using the SwissADME online tool. These findings reveal that triazole compounds based on crotonate work as α-amylase α-glucosidase enzyme inhibitors, which help in the development of novel therapies for diabetes mellitus and can serve as lead molecules in drug discovery as potential antidiabetic drugs.

4.4 Conclusion

The design, synthesis, assessment, and antidiabetic action of a new family of crotonate-based triazole derivatives (**3a-3i**) are explained in this chapter. The most significant α-amylase and α-glucosidase inhibitory activity was revealed by compounds **3b** and **3a**, which were found to be similar to standard acarbose. Halogen atoms are among the electron-removing groups that are included in these compounds. In particular, there is fluorine at the para position in the aromatic system and chlorine at the ortho position in the phenyl ring. According to a Structure-Activity Relationship (SAR) research, compounds that include a 1, 2, 4-triazole ring and electron-withdrawing halogen atoms (F, Cl) in the para and ortho positions of the aromatic system exhibited much higher activity against both enzymes. The results of molecular docking studies provide evidence for this, since they demonstrate that the compound **3b** forms three hydrogen bonds at the active site of the enzyme (4W93). The hydrogen atom that is a part of the hydrazinyl group forms a hydrogen bond with the oxygen atom that is a part of ASP197 (NH---O-ASP197, 2.21 Å). Owing to traits like as the ease with which it may be raised in laboratory environments and its diminutive size, the *Drosophila melanogaster* model has long been recognized as an important tool in research. The results demonstrated that **3b** performed better than **3a**, **3c**, and **3f** with respect to efficacy among the compounds that were recently synthesized. This may be addressed further by gradually raising the dosage, which would improve its anti-diabetic properties as a result.

Chapter 5

Synthesis, characterization, and biological assessment of bis–heterocyclic compounds containing Indole and Triazole

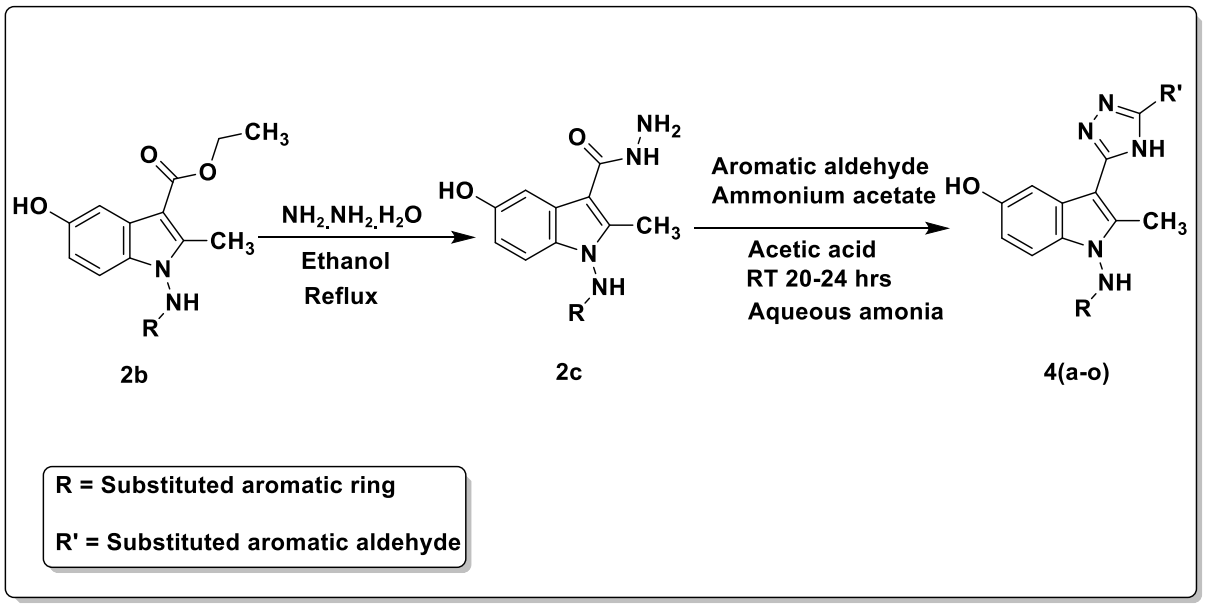
5.1 Introduction

The indole moiety, which consists of a benzene ring that is fused with four or five places of a pyrrole ring, is found in a large variety of locations across the natural world. Indole and its derivatives exhibit a diverse array of biological properties. Some of these properties include anticancer, antiviral, antioxidant, antibacterial, and antidiabetic action. A comprehensive literature study discovered that indole-based drugs and their derivatives are often used in the treatment of diabetes and other associated disorders. Consequently, fused-heterocyclic

compounds that are made up of indole and 1,2,4-triazole have been the focus of a significant amount of research due to the fact that their pharmacological potential and biological relevance make them very fascinating topics to examine. Utilizing the previously stated key facts as a basis, we created and synthesized a number of 1,2,4-triazole derivatives that included the indole moiety and then explored their α-amylase and α-glucosidase inhibitory capabilities by employing *in-vitro* and *in-vivo* techniques.

5.2 Materials and Methods

In order to develop and synthesize a variety of bis-heterocyclic compounds that comprise indole and triazole, the synthetic pathway included the production of ethyl 1-(2,4-dinitrophenylamino)-5-hydroxy-2-methyl 1*H*-indole-3-carboxylate, among other molecules. Spectroscopic methods, including ^{1}H-NMR,^{13}C-NMR, Fourier transform infrared spectroscopy (FT-IR), and liquid chromatography-mass spectrometry (LC-MS), were used to validate the substances. Antidiabetic potential was assessed by the use of *in-vitro* and *in-vivo* α-amylase and α-glucosidase inhibitory activities.



Scheme 5.1 Synthesis of bis–heterocyclic compounds containing Indole and Triazole

5.3 Results and Discussion

There were four components that constituted the majority of the newly synthesized bis-heterocyclic compounds: 1*H*-indol-5-ol moiety, 4*H*-1,2,4-triazol, aromatic ortho-para nitro groups, and a substituted phenyl group. The different chemical entities found in the phenyl

group show diverse levels of activity in the synthesized compounds once the inhibitory effect has been analyzed. A triazole ring and a benzyl moiety with different locations (Cl, F, OCH_3, and OH) have a higher ability to inhibit the enzymes α-amylase and α-glucosidase when compared to the standard drug acarbose. There are two electron-donating methoxy groups (O-CH_3) present in the chemical **4i**. These methoxy groups are connected to the ortho and meta-substituted phenyl rings. The methoxy group contains an oxygen atom that has lone pairs of electrons that can be donated into the pi system of the benzene ring through a process known as resonance. Additionally, the effect of two methoxy groups at ortho and meta-substituted phenyl rings results in increased potential inhibitory activity against α-amylase and α-glucosidase (IC_{50} = 54.68 µg/ml and IC_{50} = 59.74 µg/ml, respectively). The second greatest α-amylase inhibitory activity was shown by compound **4j**, which consists of a thiomethyl group and an electron-donating group that are bonded to a para-substituted phenyl ring (IC_{50} = 56.00 µg/ml and IC_{50} = 61.37 µg/ml). The methyl group and the lone pairs of electrons on the sulfur atom were responsible for this because of the inductive effect, which has the ability to contribute electron density to the molecule that is in the vicinity. The α-amylase and α-glucosidase enzymes were shown to be not very susceptible to the inhibitory effects of the remaining substances.

5.4 Conclusions

The structure-activity relationship demonstrates that **4i** and **4j** have a significant ability to inhibit the enzymes α-amylase and α-glucosidase *in-vitro*. In order to ascertain the efficacy of these compounds in an *in-vivo* environment, a meal comprising equal doses of either acarbose or the compounds with the greatest *in-vitro* activity was given to *Drosophila melanogaster* flies. The findings showed that standard acarbose had the strongest antihyperglycemic activity, followed by the compounds. The current study was able to identify compounds **4i** and **4j** as prospective candidates for the development of a new class of antidiabetic medications.

Outcome of Research work

- The introduction of the suggested research project took place. The incorporation of a high number of heteroatoms in conjunction with heterocyclic compounds should be an effective method of increasing both stability and biological activity. Fused heterocyclic compounds that include a significant number of N, O, and S atoms that

have been substituted, in addition to F, Cl, and other elements that have been replaced in the para and ortho positions, have the ability to inhibit or delay the digestion of carbohydrates and to decrease the pace at which glucose is absorbed from insulin into the circulation. We have predicted these molecules may have the ability to regulate hyperglycemia.

- A systematic approach was utilized for the synthesis of a new class of indole-pyrazole derivatives based on sulfonamides. The compound **2d** was found to have good inhibitory activity against α-amylase and α-glucosidase enzymes, with an IC_{50} value of 83.87 μM and an IC_{50} value of 73.15 μM, respectively, in comparison to the standard acarbose.
- In the same way, we have synthesized a number of fluorine-based derivatives of 1,3,4-oxadiazole and have characterized them. The molecule **1i** (IC_{50} = 54.83 μg/ml and IC_{50} = 60.35 μg/ml) contains an NH_2 group located in the meta position of the phenyl ring, and it exhibits strong inhibitory activity against the enzymes α-amylase and α-glucosidase. This information was discovered via research of the structure-activity connection. The findings demonstrated without a shadow of a doubt that the ortho and meta locations of the ring exhibited more inhibitory effect against the α-amylase and α-glucosidase enzymes as compared to the para positions of the phenyl ring.
- I have created new triazole derivatives that are based on the compound β-amino crotonate. The structure-activity relationship (SAR) study revealed that compounds that had a 1,2,4-triazole ring and halogen atoms that were electron-withdrawing (F, Cl) in the para and ortho positions of the aromatic system exhibited much increased activity against both enzymes. Molecular docking studies provide evidence for this.
- The *Drosophila melanogaster* model is widely regarded as an important research tool owing to characteristics like as its simple rearing in laboratory environments and its small size.
- A single research piece has been submitted to the magazine Chemistry and Biodiversity, and two research articles have been published in journals that are well-known around the world. As of right now, the final research is still in the process of being composed and is due to be submitted by October 10, 2025.

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List of Journal Publications

[1] A paper entitled "Synthesis of novel oxadiazole derivatives: DFT calculations, molecular docking studies and *In vitro, In vivo* evaluation of antidiabetic activity using *Drosophila melanogaster* model" in **Journal of the Iranian Chemical Society**, July 2024.

Govinda Anjanayya [a], Ramesh Gani [a*], Avinash Kundadka Kudva [bc], Shrinivas Joshi [d] Murigendra Hiremath [e], Apsara Kavital [e], Karabasanagouda Timanagouda [f], Basavarajaiah Mathada [g], Mohammad Javeed [h], Raifa Abdul Aziz [i], Shamprasad Varija Raghu [j], https://doi.org/10.1007/s13738-024-03067-x

[2] A paper entitled "Exploration of a Novel Indole/Pyrazole Scaffold as a Promising Dual α-Glucosidase and α-Amylase Inhibitor: an In Vitro, In Vivo and In Silico Approach Toward Antidiabetic Drug Design" in **Russian Journal of Bioorganic Chemistry,** April 2025.

Govinda Anjanayya[a], Ramesh Gania, *, Murigendra Hiremath[b], Apsara Kavital[b], Shrinivas Joshi[c], Karabasanagouda Timanagouda[d], Raifa Abdul Aziz[e], Shamprasad Varija Raghu[f], and Basavarajaiah Suliphuldevara Mathada[g] doi: 10.1134/S1068162024605391.

Communicated Papers

[1] A paper entitled "Unveiling the Potential of Novel Triazole hybrids as dual α- amylase and α-glucosidase inhibitory Activities Using the Drosophila Model: Theoretical and Experimental Insights"

Govinda Anjanayya[1], Ramesh Gani[1*], Murigendra Hiremath [2], Apsara Kavital [2], Shrinivas Joshi [3], Ravindra Malabadi[4], Raifa Abdul Aziz[5], Shamprasad Varija Raghu [5,6]. Communicated in the Chemistry and Biodiversity, Wiley Publication. **Under Review**

Papers Presented in Conferences

[1] Participated and presented a paper entitled "In vitro Alpha Amylase Inhibitor Activity of Indole Derivatives Containing Sulfonamide Group" in the 13th India-Japan Science and Technology Conclave: International Conference on Frontier Areas of Science and Technology (ICFAST-2023) jointly organized by International Affairs Cell, Shivaji University, Kolhapur and Indian JSPS Alumni Association.

Govinda Anjanayya, Ramesh S. Gani*

[2] Participated in '3rd International Conference on Physics of Material and Nano-Technology ICPN-2023' organized by Department of Physics, Mangalore University during September 21-23, 2023.

Govinda A.

[3] Participated and presented a paper entitled "Investigation of 1,3,4-oxadiazole derivatives containing fluorine as novel α-amylase and α-glucosidase inhibitors with antidiabetic activity" in the 5th International Conference on Advanced in Mechanical Engineering (ICAME 2024), organized by the Department of Mechanical Engineering, SRM Institute of Science and Technology, Kattankulathur, Tamilu Nadu, India during 20-22, March 2024.

Govinda Anjanayya, Dr. Ramesh S. Gani*

[4] Participated and presented a paper entitled "Investigation of 1,2,4-Triazole derivatives incorporated *(E)*-3-(2-(2-(2,4-dinitrophenyl) hydrazinyl) prop-1-en-1-yl as novel α-amylase inhibitor with antidiabetic activity" in the International Conference on Advances in Chemical and Physical Sciences (ICACPS-2025), organized by the School

of Physical Sciences, Amrita Vishwa Vidyapeetham, Mysuru Campus, held on 23rd and 24th January 2025

Govinda Anjanayya, Dr. Ramesh S. Gani*

[5] Participated and presented a paper entitled "Synthesis, Characterization and Antidiabetic Evaluation of novel 1, 2, 4-triazole derivatives carrying *(E)*-3-(2-(2-(2,4-dinitrophenyl) hydrazinyl) prop-1-en-1-yl." in the International Conference on Recent Advances in Chemical and Biological Sciences for Sustainable Future (RACBSF-2025) held at DSCE, Bengaluru during 19th -21st February 2025.

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[6] Participated and presented a paper entitled "Synthesis, Characterization and Antidiabetic Evaluation of novel bis–heterocyclic compounds containing Indole and Triazole" in the Two Days National Conference on Artificial Intelligence (AI)-A Multidisciplinary Approach in Research (AIMAR-2025) held at Vijaya College, Bengaluru during 11th and12th September 2025.

Govinda Anjanayya, Dr. Ramesh S. Gani*

Participated in Workshops

[1] Participated in the workshop on "Use of Dissolution Testing during drug Product Development practical hands-on training" held on 29th and 30th, August 2022 Conducted by Department of Industrial Chemistry.

[2] Participated in the workshop on "Two Days Workshop on LaTex programming'' organized by the Computer Centre, Mangalore University, held on January 18-19, 2023.

[3] Participated in the one day workshop on "Open Access Publishing'' held in the Mangalore University, on 20 June 2024.

[4] Participated in the three-days hands-on training program on "Molecular Docking: From Theory to Practical" conducted from 07-03-2025 to 09-03-2025, by Vidyothini Edutech Pvt. Ltd.

Participated in International Webinar

[1] Participated in the International Webinar on "**Nanopore Sequencing overview and Application**" by Dr. J. Sridharan, Field Application Scientist Avantor-VWR, on 17th June 2022 conducted by Centre for Research and Innovation School of Natural Science, Mandya District, Karnataka-571448 India.

[2] Participated in "WEBINAR ON: user Awareness Programme on Map MyAccess through ONOS Database and TRACXN-Private Market intelligence tool" on 12th August 20205 conducted by Mangalore University Library.

Govinda
(Research Scholar)

Dr. Ramesh S. Gani
(Research Guide)